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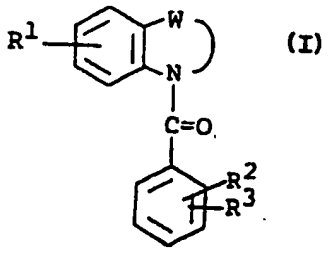
(54) Title: BENZOHETEROCYCLIC COMPOUNDS



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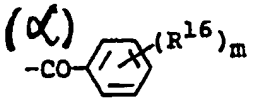


(57) Abstract

Novel benzoheterocyclic compounds of formula (I), wherein R^1 is H, halogen, alkyl, optionally substituted amino, alkoxy; R^2 is H, halogen, alkoxy, phenylalkoxy, OH, alkyl, optionally substituted amino, carbamoyl-alkoxy, optionally substituted amino-alkoxy, optionally substituted benzoyloxy; R^3 is a group: $-NR^4R^5$ or $-CO-NR^{11}R^{12}$; R^4 is H, optionally substituted benzoyl, alkyl; R^5 is a group α [R^{16} is halogen, optionally substituted alkyl, OH, alkoxy, alkanoyloxy, alkylthio, alkanoyl, carboxy, alkoxycarbonyl, CN, NO_2, optionally substituted amino, phenyl, cycloalkyl, etc., or a group: $-O-A-NR^6R^7$; m is 0 to 3], phenyl-alkoxycarbonyl, alkanoyl, phenyl-alkanoyl, etc.; R^{11} is H or alkyl; R^{12} is cycloalkyl or optionally substituted phenyl; and W is a group: $-(CH_2)_p$ (p is 3 to 5) or $-CH=CH-(CH_2)_q$ (q is 1 to 3), the carbon atom of these groups being optionally replaced by 0, S, SO, SO_2 or a group: $-N(R^{13})-$ and further these groups having optionally 1 to 3 substituents of alkyl, alkoxycarbonyl, carboxy, OH, O, alkanoyloxy, etc., which have excellent vasopressin antagonistic activies and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor, and a vasopressin antagonistic composition containing the compound as the active ingredient.

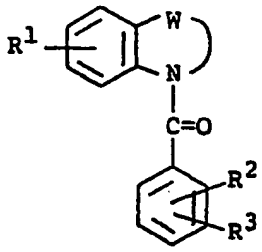
BENZOHETEROCYCLIC COMPOUNDS

Technical Field

This invention relates to novel benzoheterocyclic compounds which have excellent vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, platelet aggregation inhibitor.

Disclosure of the Invention

The benzoheterocyclic compounds of this invention have the following formula:



(1)

wherein R^1 is hydrogen atom, a halogen atom, a lower alkyl, an amino having optionally a lower alkyl substituent, or a lower alkoxy,

R^2 is hydrogen atom, a halogen atom, a lower alkoxy, a phenyl(lower)alkoxy, hydroxy, a lower alkyl, an amino having optionally a lower alkyl substituent, a carbamoyl-substituted lower alkoxy, an amino-substituted lower alkoxy having optionally a lower alkyl substituent, or a benzoyloxy which has optionally a halogen substituent on the phenyl ring,

R^3 is a group of the formula: $-N\begin{matrix}R^4\\R^5\end{matrix}$ or a group of the formula: $-C(=O)-N\begin{matrix}R^{11}\\R^{12}\end{matrix}$,

are the same or different and are each hydrogen atom, a lower alkyl, a lower alkenyl, a lower alkanoyl, a cycloalkyl, an oxiranyl-substituted lower alkyl, a lower alkyl having optionally 1 to 2 substituents selected from a lower alkoxy, hydroxy and an amino having optionally a lower alkyl substituent, a phenyl-lower alkyl, a pyridyl-lower alkyl, a lower alkylsulfonyl, benzoyl, a lower alkoxy-carbonyl, anilinocarbonyl, an aminocarbonyl having optionally a lower alkyl substituent, a cyano-substituted lower alkyl, a lower alkoxycarbonyl-substituted lower alkyl, a carbamoyl-substituted lower alkyl, a carboxy-substituted lower alkyl, a tetrahydropyranyloxy-substituted lower alkyl, a lower alkanoyloxy-substituted lower alkyl, a piperidinyl having optionally a phenyl-lower alkyl substituent on the piperidinyl ring, a halogen-substituted lower alkanoyl, an imidazolyl-substituted lower alkanoyl, an amino-lower alkanoyl having optionally a substituent selected from a lower alkyl and a lower alkoxycarbonyl, an aminocarbonyl-lower alkyl having optionally a lower alkyl substituent, or a phenyl-lower alkoxycarbonyl, or R^{14} and R^{15} may bind together with nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group with or without being intervened with nitrogen or oxygen, wherein the heterocyclic group may optionally have a substituent selected from a lower alkyl, a phenyl-lower alkyl or a lower alkanoyl).

The benzoheterocyclic compounds of the formula (1) and

their salts have excellent vasopressin antagonistic activities and vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic activity, platelet agglutination inhibitory activity and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor and are used for the prophylaxis and treatment of hypertension, edema, ascites, heart failure, renal function disorder, vasopressin parasecretion syndrome (SIADH), hepatocirrhosis, hyponatremia, hypokaliemia, diabetic, circulation disorder, and the like.

Each group in the above formula (1) includes specifically the following groups.

The "lower alkoxy" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The "lower alkyl" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, and the like.

The "halogen atom" includes fluorine atom, chlorine atom, bromine atom and iodine atome.

The "amino having optionally a lower alkyl substituent" includes an amino having optionally one or two substituents selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, amino,

(propylene glycol), ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweeting agents, and other medicaments, if required.

The amount of the active compound of this invention (active ingredient) to be incorporated into the anti-vasopressin preparations is not specified but may be selected from a broad range, but usually, it is preferably in the range of 1 to 70 % by weight, more preferably 5 to 50 % by weight.

The anti-vasopressin preparation of this invention may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intraveneously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are

administered in intrarectal route.

The dosage of the anti-vasopressin agent of this invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.6 to 50 mg of the active compound of this invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in an amount of 10 to 1000 mg per the dosage unit.

Brief Description of Drawing

Fig. 1 to Fig. 4 show a chart of NMR ($CDCl_3$) of the compounds in Examples 978 and 979.

Best Mode for Carrying Out the Invention

The present invention is illustrated by the following Preparations of anti-vasopressin agent, Reference Examples of processes for preparing the starting compounds to be used for preparing the active compounds, Examples of processes for preparing the active compounds, and Experiments of the activities of the active compounds of this invention.

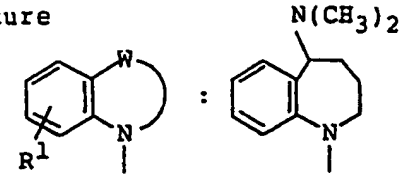
Preparation 1

Film coated tablets are prepared from the following components.

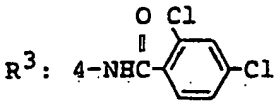
Components	Amount
4-Methylamino-1-[4-(3,5-dichlorobenzoyl-amino)benzoyl]-1,2,3,4-tetrahydroquinoline	150 g

Example 407

Structure



R^2: H



Crystalline form: White powder

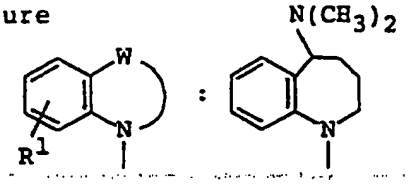
Recrystallization solvent: Ethanol

Melting Point: 181 - 183°C

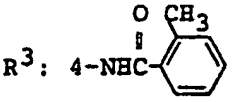
Form: Free

Example 408

Structure



R^2: H



Crystalline form: White powder

Recrystallization solvent: Ethanol

Melting Point: 207 - 208°C

Form: Free